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L21 ANSWER 163 OF 174 CAPLUS COPYRIGHT 2002 ACS
AN 1993:546365 CAPLUS
DN 119:146365
TI **Cinnamic** acids and **skin-lightening** cosmetics containing them
IN Oonuma, Hiroaki; Nishizawa, Yoshinori; Jokura, Hiroko; Kobayashi, Takeshi; Imokawa, Genji
PA Kao Corp, Japan
SO Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 05105643	A2	19930427	JP 1991-266408	19911015

OS MARPAT 119:146365

AB **Skin-lightening** cosmetics contain **cinnamic** acids I (R1 = H, lower acyl; R2 = lower alkyl; R3 = H, lower alkyl) as active ingredients. (Carbethoxymethylene)triphenylphosphorane was added to C6H6 soln. contg. 4-hydroxy-2-methoxybenzaldehyde at room temp. within 1 h and the mixt. was stirred for another 3 h to give 68% Et 4-hydroxy-2-methoxycinnamate, which was stirred with Ac2O-pyridine at room temp. for 1 night to give 96% Et 4-acetoxy-2-methoxycinnamate (II). EtOH-H2O contg. 5% II was applied to guinea pigs to show melanin formation inhibition. A cosmetic lotion contg. I 5.0, glycerin 4.0, polyoxyethylene hydrogenated castor oil 1.5, EtOH 10.0, Na pyrrolidonecarboxylate 2.0, perfume, and H2O to 100.0 wt.% was formulated.

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CLIPPEDIMAGE= JP405105643A
PAT-NO: JP405105643A
DOCUMENT-IDENTIFIER: JP 05105643 A
TITLE: CINNAMIC ACID DERIVATIVE AND SKIN-BEAUTIFYING COSMETIC CONTAINING THE
DERIVATIVE AS ACTIVE COMPONENT

PUBN-DATE: April 27, 1993

INVENTOR-INFORMATION:
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JOKURA, HIROKO
KOBAYASHI, TAKESHI
IMOKAWA, GENJI

ASSIGNEE-INFORMATION:
NAME COUNTRY
KAO CORP N/A

APPL-NO: JP03266408
APPL-DATE: October 15, 1991

INT-CL_(IPC): C07C069/145; A61K007/00 ; A61K007/48 ; C07C069/734 ; C07C059/52
US-CL-CURRENT: 424/401,560/55

ABSTRACT:
PURPOSE: To provide a safe skin-beautifying cosmetic having excellent pigmentation improving effect and effective for treating and improving the pigmented part such as spots, freckles and sunburnt skin to the normal skin color by topically applying the cosmetic to the pigmented part.

CONSTITUTION: A cinnamic acid derivative of formula (R<SB>1</SB> is H or lower
acyl; R<SB>2</SB> is lower alkyl; R<SB>3</SB> is H or lower alkyl), preferably
4-hydroxy-2'- methoxycinnamic acid, 4-acetoxy-2-methoxycinnamic acid or their
ester, etc., especially 4-acetoxy-2-methoxycinnamic acid ethyl ester is compounded to a skin-beautifying cosmetic as an active component in an amount
of preferably 0.01-50wt.%, especially 0.1-20wt.% to obtain the objective skin-beautifying cosmetic having the above effect different from conventional sun-screening agent to prevent the sunburn. The cosmetic is free from irritation to the skin and development of allergy, etc., and has high safety. The preferable amount of the active component per 1cm<SP>2</SP> of the skin is
1-20mg for creamy or ointment preparation and 1-10mg for liquid preparation.

DERWENT-ACC-NO: 1993-172638
DERWENT-WEEK: 199321

TITLE: Whitening cosmetic contg. cinnamic acid deriv. - e.g. 4-acetoxy-2-methoxy cinnamic acid, having therapeutic effect on sun-burned skin
PATENT-ASSIGNEE: KAO CORP[KAOS]
PRIORITY-DATA: 1991JP-0266408 (October 15, 1991)
PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 05105643 A	April 27, 1993	N/A	007	C07C 069/145

APPLICATION-DATA:

PUB-NO	APPL-DESCRIPTOR	APPL-NO	APPL-DATE
JP05105643A	N/A	1991JP-0266408	October 15, 1991

INT-CL_(IPC): A61K007/48; C07C059/52 ; C07C069/145 ; C07C069/734
ABSTRACTED-PUB-NO: JP05105643A
BASIC-ABSTRACT: Whitening cosmetics contain a cinnamic acid deriv. of formula
(1) as the effective component. R1 = H or lower acyl; R2 = lower alkyl; R3 = H
or lower alkyl.

USE/ADVANTAGE - The whitening cosmetics have excellent chromopexy preventing
effect. Unlike conventional sun-screen agents preventing sun-tan, the whitening cosmetic shows therapeutic effects on sun-burned skin by applying topically onto the sun-burned area. (1) does not irritate the skin and does not cause allergy, thus being usable with high safety.

In an example, a mixt. of 300 mg (1.35 mmol) of ethyl ester of 4-hydroxy-2-methoxy cinnamic acid, 220 mg (2.15 mmol) of acetic anhydride and
1.07 g of pyridine was stirred overnight at room temp.. To the reaction mixt. was added 10 ml of water, and mixt. subjected to extn. with 20 ml of ethyl acetate twice, followed by drying over Mg sulphate. The solvent was distilled
off by means of evaporator. The residue was purified by means of a column chromatography (SiO_2, hexane/ethyl acetate = 5) to afford 341 mg (1.29 mmol) of
ethyl ester of 4-acetoxy-2-methoxy cinnamic acid as white crystals, m.pt. 56.4-57.0 deg. C.
CHOSEN-DRAWING: Dwg.0/0
DERWENT-CLASS: B05 D21 E14
CPI-CODES: B10-C03; B10-C04C; B10-G02; B12-A07; B12-L02; B12-L08; D08-B;
D08-B09A; E10-C03; E10-E02D2; E10-G02A;

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JP 05105643 A

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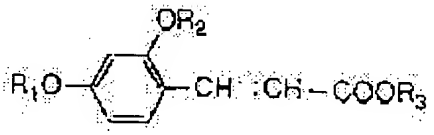
A61K 7/48
C07C 69/734
// C07C 59/52

(21)Application number : **03-266408**
(22)Date of filing : **15.10.1991**

(71)Applicant : **KAO CORP**
(72)Inventor : **ONUMA HIROAKI**
NISHIZAWA YOSHINORI
JOKURA HIROKO
KOBAYASHI TAKESHI
IMOKAWA GENJI

(54) CINNAMIC ACID DERIVATIVE AND SKIN-BEAUTIFYING COSMETIC CONTAINING THE DERIVATIVE AS ACTIVE COMPONENT

(57)Abstract:
PURPOSE: To provide a safe skin-beautifying cosmetic having excellent pigmentation improving effect and effective for treating and improving the pigmented part such as spots, freckles and sunburnt skin to the normal skin color by topically applying the cosmetic to the pigmented part.
CONSTITUTION: A cinnamic acid derivative of formula (R1 is H or lower acyl; R2 is lower alkyl; R3 is H or lower alkyl), preferably 4-hydroxy-2'-methoxycinnamic acid, 4-acetoxy-2-methoxycinnamic acid or their ester, etc., especially 4-acetoxy-2-methoxycinnamic acid ethyl ester is compounded to a skin-beautifying cosmetic as an active component in an amount of preferably 0.01-50wt.%, especially 0.1-20wt.% to obtain the objective skin-beautifying cosmetic having the above effect different from conventional sun-screening agent to prevent the sunburn. The cosmetic is free from irritation to the skin and development of allergy, etc., and has high safety. The preferable amount of the active component per 1cm2 of the skin is 1-20mg for creamy or ointment preparation and 1-10mg for liquid preparation.



LEGAL STATUS

[Date of request for examination]

[Date of sending the examiner's decision of rejection]

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[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of rejection]

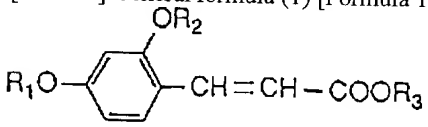
[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

* NOTICES *

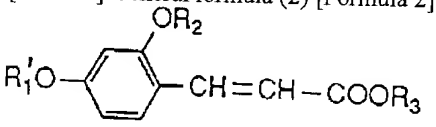
CLAIMS

[Claim(s)]
[Claim 1] General formula (1) [Formula 1]



(1)

They are the whitening cosmetics which make an active principle the cinnamic acid derivative expressed with (in the inside of a formula, and R1 R2 shows a low-grade alkyl group, and R3 shows a hydrogen atom or a low-grade alkyl group for a hydrogen atom or a low-grade acyl group).
[Claim 2] General formula (2) [Formula 2]



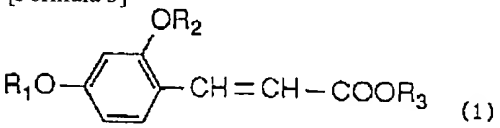
(2)

It is the cinnamic acid derivative expressed with (in inside [of a formula], and R1' R2 shows a low-grade alkyl group, and R3 shows a hydrogen atom or a low-grade alkyl group for a low-grade acyl group).

[Translation done.]

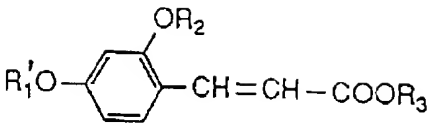
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] this invention is safe and relates to the new cinnamic acid derivative which are the whitening cosmetics excellent in the pigmentation improvement effect, and its active principle.
[0002]
[Description of the Prior Art] Follow the pigmentation after a stain, a freckle, and suntan on an aging, it seldom occurs, increases or comes to disappear, and serves as the trouble to the middle-aged and the elderly's skin. Although it is not [the sideration device of these hemochromatosis] yet clear, it is considered because the melanin synthesis function in an epidermis melanocyte rose by the solar beam of light especially ultraviolet rays, and operation of melanocyte tropic hormones etc. Moreover, cornification retardation-ization accompanied by the aging of a keratinocyte (keratinocyte) also delays the passage speed to the outside of epidermis, and is considered to discover the increase in the melanin-granule density in epidermis, i.e., the symptom which a pigmentation increases clinically, together with sthenia of melanin synthesis ability. Furthermore, those pigmentation sections exist locally and it is also considered the result which made the device in which local melanin synthesis sthenia of a melanocyte or melanin synthesis of a melanocyte was controlled modulate from differentiation arising clearly with surrounding normal skin color.
[0003] These acquired coloring matter, i.e., the medicine which makes even normal skin color recover the self-possessed section of melanin, is desired strongly, and many medicines were developed until now and it has been commercialized. For example, although the charge of makeup using the vitamin-C (L ascorbic acid) derivative which has the outstanding reduction ability in recent years had also been used, while difficulty was in the stability, the present condition was that an effect hardly accepts in external application.
[0004] On the other hand, although used as a medicine, like hydroquinone makes the treatment and the Negro skin of a stain white in the West, there is a problem in blending as a medicine from points, like there are this and a case where a problem is in the safety (stimulative, allergy nature) of the matter [itself], and a facula is produced. In addition, although various melanin inhibitors are reported, as a cinnamic acid derivative, p-hydroxy cinnamic acid (Brun, J.Soc.Cosmet.Chem., 25, and 61 (1974)) and the p-hydroxy cinnamic acid amide derivative (JP,62-56459,A) are known. However, the present condition is that the matter with which it is satisfied of both of safety to the pigmentation improvement effect and the skin enough is not known.
[0005]
[Problem(s) to be Solved by the Invention] It is safe and this invention aims at offering the whitening cosmetics excellent in the pigmentation improvement effect.
[0006]
[Means for Solving the Problem] As a result of inquiring zealously that this invention persons should get the matter which it lets matter] a research of a melanin generation device pass, and decreases or vanishes a pigmentation, a specific cinnamic acid derivative has melanin generation depressant action, found out that a manifestation of stimulative and allergy to the skin etc. moreover did not accept, and completed this invention.
[0007] That is, this invention is general formula (1) [0008] of a degree.
[Formula 3]



(1)

[0009] The whitening cosmetics which make an active principle the cinnamic acid derivative expressed with (in the inside of a formula and R1 R2 shows a low-grade alkyl group, and R3 shows a hydrogen atom or a low-grade alkyl group for a hydrogen atom or a low-grade acyl group) are offered.
[0010] Moreover, general formula (2) [0011] among the active principle
[Formula 4]



(2)

[0012] The cinnamic acid derivative expressed with (R1' has the meaning as the above with R2 and R3 for a low-grade acyl group among a formula) is also offered. [same]
[0013] As a cinnamic acid derivative (1) used in this invention, 4-hydroxy-2-methoxy cinnamic acid or its ester, 4-acetoxy-2-methoxy cinnamic acid, or its ester is mentioned as a desirable thing, for example. As a suitable compound, 4-acetoxy-2-methoxy ethyl-cinnamate ester can be mentioned especially.
[0014] The cinnamic acid derivative (1) of this invention is compoundable according to it according to technique given in reference. For example, a 4-hydroxy-2-methoxy benzaldehyde system compound, a malonic acid, or its ester is made to condense under presence of bases, such as a pyridine. the technique of making it convert into a derivative by the technique of hydrolysis and (or) common use if needed -- a 4-hydroxy-2-methoxy benzaldehyde system compound and Wittig reagents, such as a triphenyl (cull ******** methylene) phosphorane, are made to condense, and it can obtain easily by the technique of making it convert into a derivative by the technique of hydrolysis and (or) common use if needed etc.
[0015] It is independent, or the above-mentioned cinnamic acid derivative (1) can be blended with the whitening cosmetics of this invention combining two or more sorts, and the loadings have 0.1 - 20 preferably desirable % of the weight 0.01 to 50% of the weight in a constituent.
[0016] Although the whitening cosmetics of this invention can be made into various gestalt, generally it is desirable to consider as the charges of makeup, such as the shape of the shape of the shape of the shape of the shape of the shape of a lotion and a milky lotion and a cream and salve and a stick, the shape of a solution by the organic solvent, the letter of a pack, and gel.
[0017] Arbitrary components other than a cinnamic acid derivative (1) can be blended with the whitening cosmetics of this invention in the domain which does not spoil the effect of this invention, and the component usually blended with the charge of makeup, for example, a purified water, ethanol, an oily matter, a **** agent, a thickener, antiseptics, an emulsifier, a **** component, fine particles, perfume, emulsion stabilizer, pH regulator, etc. can be blended with them according to the pharmaceutical form. As an oily component, specifically A liquid paraffin, vaseline, a paraffine wax, Squalane, yellow bees wax, a carnauba wax, olive oil, lanolin, higher alcohol, The synthetic ester oil of a fatty acid, and higher alcohol and a fatty acid, silicon oil, etc. are mentioned. As a **** agent, a sorbitol, a xylitol, a glycerol, a maltitol, A propylene glycol, 1, 3-butylene glycol, 1, 4-butylene glycol, Pyrrolidone carboxylic-acid sodium, a lactic acid, a sodium lactate, polyoxypropylene fatty acid ester, A polyethylene glycol etc. is mentioned. as a thickener A carboxyvinyl polymer, A carboxymethyl cellulose, polyvinyl alcohol, a carrageenan, Electrolytes, such as water soluble polymers, such as gelatin, a sodium chloride, and potassium chloride, etc. are mentioned. As antiseptics, a urea, the methylparaben, an ethylparaben, a propylparaben, The butylparaben, a sodium benzoate, etc. are mentioned. as an emulsifier Polyoxyethylene alkyl ether, Polyoxyethylene fatty acid ester, polyoxyethylene sorbitan fatty acid ester, A glycerine fatty acid ester, polyglyceryl fatty acid ester, polyoxyethylene glycerine fatty acid ester, Nonionic surface active agents, such as polyoxyethylene hydrogenated castor oil and polyoxyethylene sorbitol fatty acid ester, are mentioned. As fine particles, talc, a sericite, a mica, a kaolin, a silica, a bentonite, A vermiculite, a zinc white, a mica, mica titanium, titanium oxide, a magnesium oxide, a zirconium oxide, a barium sulfate, red ocher, an iron oxide, ultramarine blue, etc. are mentioned, and buffers, such as a lactic-acid-sodium lactate and a citric-acid-sodium citrate, are mentioned as a pH regulator. Moreover, as various active principles, enhancement in a melanin depressor effect can be aimed at by adding an allantoin, vitamin-E acetate, glycyrrhizin, a coix seed, various vegetable extracts, etc. Furthermore, it can also consider as the charge of makeup which had the prevention effect and curative effect of suntan by adding various ultraviolet-absorption matter.
[0018] By applying to the affected parts, such as the inflammation of the skin by ultraviolet rays, a stain, a freckle, and the pigmentation section after suntan, locally, the whitening cosmetics of this invention can treat and improve this site, and can return it to normal skin color. Moreover, generally in the case of the tablet of the shape of the shape for example, of a cream, or salve, it is [1cm of skin sides] desirable [the dosage] in the case of 1-20mg per two, and a liquefied tablet to be referred to as 1-10mg similarly.
[0019]
[Example] Next, an example and the example of reference are given and this invention is explained.
[0020] Synthetic :4-hydroxy-2-methoxy benzaldehyde 0.5g (3.3mmol) of example of reference 14-hydroxy-2-methoxy ethyl-cinnamate ester was melted to benzene 23ml, and, in addition, churning was continued for bottom (cull ******** methylene) triphenyl phosphorane of room temperature 1.64g (4.7mmol) in the status over 1 hour for 3 hours. After the reaction end, after distilling off benzene by the evaporator, the residue was covered over column chromatography (silica gel), and was refined, and 0.7g of rough refining objects was obtained. The recrystallization of this was carried out from water-ethanol, and 4-hydroxy-2-methoxy ethyl-cinnamate ester 496mg (2.2mmol) was obtained as white needlelike ** of 143.1-146.0 degrees C of the melting points (68% of yield).
IR (KBr, cm-1) (s)3364, 3080, 2980, 2944, and 1682 (s), 1610 (s), 1582 (s), 1480, 1436, 1372, 1350, and 1312 (s), 1286, 1238, 1186 (s), 1168, 1112, 1038, 988, 960, 860, 800, 672, 652, 518, and 4701H-NMR7.90 (1H, d, J= 16.1Hz) (CDCl3+ D2 O, TMS, delta), 7.37 (1H, d, J= 9.0Hz) and 6.5- 6.3 (3H), 4.25 (2H, q, J= 7.2Hz), 3.85 (3H, s), 1.33 (3H, t, J= 7.2Hz), and
[0021] Mixture (synthetic :4-hydroxy-2-methoxy ethyl-cinnamate ester 300mg (1.35mmol) of example 14-acetoxy-2-methoxy

ethyl-cinnamate ester and 220mg [of acetic anhydrides] (2.15mmol) and pyridine 1.07g) was agitated at the room temperature overnight. 10ml of water was added to this, 20ml of ethyl acetate extracted twice, and it dried with magnesium sulfate. After distilling off a solvent by the evaporator, the residue was covered over the column chromatography (SiO2, a hexane / ethyl-acetate =5), and was refined, and 4-acetoxy-2-methoxy ethyl-cinnamate ester 341mg (1.29mmol) was obtained as a white crystal of 56.4-57.0 degrees C of the melting points (96% of yield).
1H-NMR7.92 (1H, d, J= 16.1Hz) (CDCl3, TMS, delta), 7.50 (1H, d, J= 8.3Hz) and 6.8- 6.6 (2H), 6.49 (1H, d, J= 16.1Hz), 4.26 (1H, q, J= 7.2Hz), and 3.87 (3H, s), 2.31 (3H, s) and 1.33 (3H, t, J= 7.2Hz) [0022] Heating churning of synthetic :4-acetoxy-2-methoxy benzaldehyde 0.86g [of example 24-acetoxy-2-methoxy cinnamic acid and 4-hydroxy-2-methoxy cinnamic acid] (4.43mmol), 1.15g [of malonic acids] (11.1mmol), and pyridine 4ml and the mixture of one drop of piperidine was carried out for 1.5 hours. The crystal which added 30ml of water and separated after churning for 30 minutes was ****ed after cooling. 295mg (1.25mmol) of 4-acetoxy-2-methoxy cinnamic acid was obtained from the 1st ** as a white crystal of 187.1-193.4 degrees C of the melting points (28% of yield).
1H-NMR12.34 (1H, brs) (DMSOd6, TMS, delta), 7.78 (1H, d, J= 16.1Hz), 7.72 (1H, d, J= 8.5Hz), 6.91 (1H, s), 6.77 (1H, d, J= 8.5Hz), 6.50 (1H, d, J= 16.1Hz), 3.85 (3H, s), and 2.28 (3H, s) -- 399mg of the mixture of 4-acetoxy-2-methoxy cinnamic acid and 4-hydroxy-2-methoxy cinnamic acid was again obtained from the 2nd ** Then, heating churning of 399mg of this mixture and the sodium-methylate 200mg (3.70mmol) methanol solution was carried out for 30 minutes. After cooling, after having added the saturated ammonium chloride solution and making it acid, it extracted by tetrahydrofuran 20ml. After distilling off a solvent by the evaporator, it melted in the ether, the saturation sodium-hydrogencarbonate aqueous solution was added, and the organic layer was separated. After having added the diluted hydrochloric acid to the water layer and making it acid, the separated yellowish green crystal was ****ed. The recrystallization of this was carried out from the water-acetone, and 114.6mg (0.52mmol) of 4-hydroxy-2-methoxy cinnamic acid was obtained as fine yellow powder of 165.5-167.5 degrees C (decomposition) of the melting points (yield is 12% to a 4-acetoxy-2-methoxy benzaldehyde).
1H-NMR (DMSOd6, TMS, delta)10.12 (1H, brs), 7.73 (1H, d, J= 16.1Hz), 7.49 (1H, d, J= 8.3Hz), 6.44 (1H, s), 6.40 (1H, d, J= 8.3Hz), 6.29 (1H, d, J= 16.1Hz), and 3.80 (3H, s) [0023] Example 3 Charge of face toilet type makeup : (composition)
4-acetoxy-2-methoxy ethyl-cinnamate ester 5.0 (weight %) Glycerol 4.0 Polyoxyethylene hydrogenated castor oil 1.5 Ethanol 10.0 Pyrrolidone carboxylic-acid sodium 2.0 Perfume Minute amount Purified water Residue Sum 100.0 [0024] Example 4 Charge of oil essence type makeup : (composition)
4-acetoxy-2-methoxy ethyl-cinnamate ester 5.0 (weight %) Mink oil 55.0 Wheat germ oil 40.0 Sum 100.0 [0025] Example 5 W/charge of O type moisture cream type makeup : (composition)
4-acetoxy-2-methoxy cinnamic acid 5.0 (weight %) Vaseline 6.0 Cholesterol 0.6 Cetanol 0.5 Sorbitansesquiolate 2.0 Liquefied lanolin 4.0 Isopropyl palmitate 8.0 Squalene 10.0 Solid paraffin 4.0 Butylparaben 0.1 Methylparaben 0.1 Glycerol 3.0 Perfume 0.2 Purified water Balance Sum 100.0 [0026] Example 6 O/charge of W type moisture cream type makeup : (composition)
4-hydroxy-2-methoxy ethyl-cinnamate ester 5.0 (weight %) Stearin acid 2.0 Cetanol 4.0 Vaseline 5.0 Squalene 8.0 Hardening palm oil 4.0 Polyoxyethylenesorbitan monostearate (20E.O.) 1.4 Lipophilic type glyceryl monostearate 2.4 Butylparaben 0.1 Methylparaben 0.1 Glycerol 3.0 Dipropylene glycol 3.0 The L-arginine 10.0 (%) potassium hydroxide 0.2 Perfume 0.2 Purified water Balance 100.0 of a total [0027] Example 7 Charge of milky lotion type makeup : (composition)
4-hydroxy-2-methoxy ethyl-cinnamate ester 5.0 (weight %) Stearin acid 1.0 Cetanol 2.0 Vaseline 2.5 Squalene 4.0 Hardening palm oil 2.0 Polyoxyethylenesorbitan monostearate (20E.O.) 1.4 Lipophilic type glyceryl monostearate 1.2 Butylparaben 0.1 Methylparaben 0.1 Glycerol 3.0 Dipropylene glycol 3.0 Potassium hydroxide 0.2 Carboxyvinyl polymer 0.2 Perfume 0.2 Purified water Balance 100.0 of a total [0028] Example 8 Charge of packed type makeup (paste-like peeled off type) : (composition)
4-hydroxy-2-methoxy cinnamic acid 10.0 (weight %) Polyvinyl alcohol 12.0 Carboxymethylcellulose sodium 3.0 Dipropylene glycol 2.0 Glycerol 2.0 Ethanol 5.0 Olive oil 3.0 Polyoxyethylene hydrogenated castor oil (30E.O.) 0.5 titanium oxide 8.0 Kaolin 6.0 Perfume 0.1 Methylparaben 0.1 Purified water Balance Sum 100.0 [0029] Example 9 Charge of salve type makeup : (composition)
4-acetoxy-2-methoxy ethyl-cinnamate ester 10.0 (weight %) White vaseline 90.0 Sum 100.0 [0030] Example 10 Charge of solution type makeup : (composition)
4-acetoxy-2-methoxy ethyl-cinnamate ester 5.0 (weight %) Ethanol 95.0 Sum 100.0 [0031] The regions-of-back hair follicle of the C57BL system mouse on eight - after-the-birth the 11th which is performing briskly the evaluation test-method:melanin synthesis by the tyrosinase activity of an example of examination 1 mouse regions-of-back skin hair-follicle organ-culture system was cultivated for three - four days. It added so that an evaluation sample might be set to last concentration 5mM to the culture medium under incubation, and the enzyme and tyrosinase activity which bears melanin synthesis were measured with the amount (3HOH) of disengagement tritiums from a 3 and 5-3H-thyrosin, and it evaluated as compared with control. The result is shown in Table 1.
He has no depressor effect. 00 - 5% **5 - 35% +35%- ++ result : [0032]
[Table 1]

	抑制効果
4-ヒドロキシ-2-メトキシ桂皮酸エチルエステル	+
4-アセトキシ-2-メトキシ桂皮酸エチルエステル	++
4-ヒドロキシ-2-メトキシ桂皮酸	±
4-アセトキシ-2-メトキシ桂皮酸	±
p-ヒドロキシ桂皮酸（比較例）	0

[0033] the example 2 of an examination -- the fading improvement effect over a pigmentation was investigated after forming a pigmentation, using the brown guinea pig which has acquired melanin maculation ability as a laboratory animal
Test-method: Using the brown guinea pig (guinea pig which skin color is similar with yellow-skinned races' thing, and coloring matter spots will begin to produce like human being in abbreviation four days after irradiation of ultraviolet rays, and will carry out a melanism most in about eight days), regions-of-back hair of this guinea pig was ****ed by hair clipper, and it ****ed with the electric shaver further. UVA (BLB lamp, 3.1mW/cm2) was irradiated for 5 minutes after injecting 8-methoxy psoralen (PUVA) intraperitoneally to this guinea pig. From the 15 days back of irradiation, produced PUVA coloring matter maculation site was followed between a total of 1 30 days twice per day, and 5% solution (ethanol 80%, 20% of water) of an evaluation sample (4-acetoxy-2-methoxy ethyl-cinnamate ester) was applied to it. The macro-scopic judging of the photographic density of skin color was carried out in the criterion shown below, it averaged the evaluating point, and measured the effect. This result is shown in Table 2.
Criterion 0: Don't accept a pigmentation.
1: Don't twist indistinctly [boundary] but accept a kana pigmentation.
2: a boundary -- accept the pigmentation of a degree clear middle
3: a boundary -- accept the pigmentation of a clear intensity
Result : [0034]
[Table 2]

	塗布前	30日後
4-アセトキシ-2-メトキシ桂皮酸エチルエステル	2.5	1.4
対照（エタノールのみを塗布）	2.4	2.2

[0035]
[Effect of the Invention] The whitening cosmetics of this invention are excellent in the pigmentation improvement effect, differ in the conventional sun block which prevents suntan beforehand, by applying to the stain of the skin, a freckle, and the pigmentation section after suntan locally, can treat and improve this site and can return it to normal skin color. Moreover, a manifestation of stimulative and allergy etc. does not accept, but the whitening cosmetics of safety of this invention are high. [as opposed to the skin in the cinnamic acid ester derivative (1) of this invention which is an active principle]

[Translation done.]

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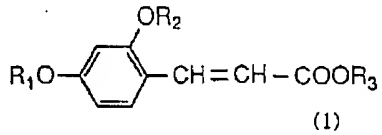
(54)【発明の名称】　桂皮酸誘導体およびこれを有効成分とする美白化粧料

(57)【要約】
【構成】　一般式(1)
【化１】

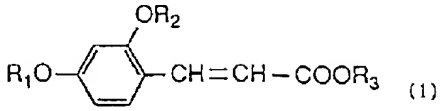


(1)

（式中、R_1は水素原子または低級アシル基を、R_2は低級アルキル基を、R_3は水素原子または低級アルキル基を示す）で表わされる桂皮酸誘導体を有効成分とする美白化粧料。
【効果】　本発明の美白化粧料は、色素沈着改善効果に優れ、皮膚のしみ、そばかす、日焼け後の色素沈着部に局所的に適用することにより、該部位を治療・改善し、正常な皮膚色に戻すことができる。また皮膚に対する刺激性、アレルギーの発現等も認められず、安全性の高いものである。

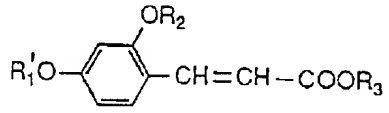
1

【特許請求の範囲】
【請求項１】　一般式(1)
【化１】



(1)

（式中、R_1は水素原子または低級アシル基を、R_2は低級アルキル基を、R_3は水素原子または低級アルキル基を示す）で表わされる桂皮酸誘導体を有効成分とする美白化粧料。
【請求項２】　一般式(2)
【化２】

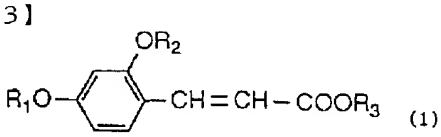


(2)

（式中、R_1'は低級アシル基を、R_2は低級アルキル基を、R_3は水素原子または低級アルキル基を示す）で表わされる桂皮酸誘導体。
【発明の詳細な説明】
【０００１】
【産業上の利用分野】本発明は、安全でかつ色素沈着改善効果に優れた美白化粧料及びその有効成分である新規な桂皮酸誘導体に関する。
【０００２】
【従来の技術】しみ、そばかすおよび日焼け後の色素沈着は、加齢に伴い発生、増加あるいは消失しにくくなり、中高年齢層の肌の悩みとなっている。これらの色素沈着症の発症機構は、未だ明確にはされていないが、太陽光線、特に紫外線や、メラノサイト刺激ホルモン等の作用により、表皮メラノサイトでのメラニン合成機能が亢進したためと考えられる。また、表皮角化細胞（ケラチノサイト）の加齢に伴う角化遅延化も、表皮外への排泄速度を遅延させ、メラニン合成能の亢進と合わせて、表皮内のメラニン顆粒密度の増加、即ち臨床的に色素沈着が増加する症状を発現するものと考えられる。更にそれらの色素沈着部は局部的に存在し、周囲の正常皮膚色と明らかに差異が生ずることより、メラノサイトの局部的なメラニン合成亢進、あるいはメラノサイトのメラニン合成をコントロールする機構を変調せしめた結果とも考えられる。
【０００３】これらの後天的な色素、即ちメラニンの沈着部を正常な皮膚色にまで回復させる薬剤が強く望まれており、これまでにも多くの薬剤が開発され商品化されてきた。例えば、近年、優れた還元能を有するビタミンＣ（L-アスコルビン酸）誘導体を用いた化粧料も用いられてきたが、安定性に難があるとともに、外用では効果がほとんど認められないのが現状であった。
【０００４】一方、欧米において、ハイドロキノンがしみの治療や黒人皮膚を白くする等の薬剤として用いられているが、これも物質自体の安全性（刺激性、アレルギー性）に問題があり、また白斑を生じさせるケースもあるなどの点から薬剤として配合することには問題がある。その他にも種々のメラニン抑制剤が報告されているが、桂皮酸誘導体としては、p-ヒドロキシ桂皮酸（Brun, J. Soc. Cosmet. Chem., 25, 61(1974)）やp-ヒドロキシ桂皮酸アミド誘導体（特開昭62-56459号公報）が知られている。しかしながら、色素沈着改善効果及び皮膚に対する安全性の両者を充分満足する物質は知られていないのが現状である。

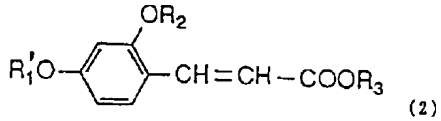
2

【０００５】
【発明が解決しようとする課題】本発明は、安全でかつ色素沈着改善効果に優れた美白化粧料を提供することを目的とする。
【０００６】
【課題を解決するための手段】本発明者らは、メラニン生成機構の研究を通して色素沈着を減少あるいは消失させる物質を得るべく鋭意検討した結果、特定の桂皮酸誘導体はメラニン生成抑制作用を有し、しかも皮膚に対する刺激性、アレルギーの発現等が認められないことを見出し、本発明を完成した。
【０００７】すなわち、本発明は次の一般式(1)
【０００８】
【化３】



(1)

【０００９】（式中、R_1は水素原子または低級アシル基を、R_2は低級アルキル基を、R_3は水素原子または低級アルキル基を示す）で表わされる桂皮酸誘導体を有効成分とする美白化粧料を提供するものである。
【００１０】また、その有効成分のうち、一般式(2)
【００１１】
【化４】



(2)

【００１２】（式中、R_1'は低級アシル基を、R_2およびR_3は上記と同様の意味を有する）で表わされる桂皮酸誘導体をも提供するものである。
【００１３】本発明において用いられる桂皮酸誘導体(1)としては、例えば、4-ヒドロキシ-2-メトキシ桂皮酸またはそのエステル、4-アセトキシ-2-メトキシ桂皮酸またはそのエステルなどが好ましいものとして挙げられる。特に好適な化合物としては、4-アセトキシ-2-メトキシ桂皮酸エチルエステルを挙げることができる。
【００１４】本発明の桂皮酸誘導体(1)は、文献記載の

方法に従って、あるいはそれに準じて合成でき、例えば、4-ヒドロキシ-2-メトキシベンズアルデヒド系化合物とマロン酸またはそのエステルをピリジン等の塩基の存在下で縮合させ、必要に応じて加水分解および（または）慣用の方法で誘導体に転化させる方法、4-ヒドロキシ-2-メトキシベンズアルデヒド系化合物と（カルベトキシメチレン）トリフェニルフォスフォラン等のウィティッヒ試薬を縮合させ、必要に応じて加水分解および（または）慣用の方法で誘導体に転化させる方法等によって容易に得ることができる。

【００１５】本発明の美白化粧料には、上記桂皮酸誘導体(1)を、単独で、または二種以上を組み合わせて配合することができ、その配合量は、組成物中に0.01～50重量%、好ましくは0.1～20重量%が好ましい。

【００１６】本発明の美白化粧料は、種々の形態にすることができるが、一般には、ローション状、乳液状、クリーム状、軟膏状、スティック状、有機溶媒による溶液状、パック状、ゲル状等の化粧料とするのが好ましい。

【００１７】本発明の美白化粧料には、本発明の効果を損ねない範囲で桂皮酸誘導体(1)以外の任意の成分を配合することができ、その剤型に応じて、化粧料に通常配合される成分、例えば精製水、エタノール、油性物質、保湿剤、増粘剤、防腐剤、乳化剤、薬効成分、粉体、香料、乳化安定剤、pH調整剤等を配合することができる。具体的には、油性成分としては流動パラフィン、ワセリン、パラフィンワックス、スクワラン、ミツロウ、カルナウバロウ、オリーブ油、ラノリン、高級アルコール、脂肪酸、高級アルコールと脂肪酸の合成エステル油、シリコーン油等が挙げられ、保湿剤としてはソルビトール、キシリトール、グリセリン、マルチトール、プロピレングリコール、1,3-ブチレングリコール、1,4-ブチレングリコール、ピロリドンカルボン酸ナトリウム、乳酸、乳酸ナトリウム、ポリオキシプロピレン脂肪酸エステル、ポリエチレングリコール等が挙げられ、増粘剤としてはカルボキシビニルポリマー、カルボキシメチルセルロース、ポリビニルアルコール、カラギーナン、ゼラチン等の水溶性高分子、塩化ナトリウム、塩化カリウム等の電解質などが挙げられ、防腐剤としては尿素、メチルパラベン、エチルパラベン、プロピルパラベン、ブチルパラベン、安息香酸ナトリウム等が挙げられ、乳化剤としてはポリオキシエチレンアルキルエーテル、ポリオキシエチレン脂肪酸エステル、ポリオキシエチレンソルビタン脂肪酸エステル、グリセリン脂肪酸エステル、ポリグリセリン脂肪酸エステル、ポリオキシエチレングリセリン脂肪酸エステル、ポリオキシエチレン硬化ヒマシ油、ポリオキシエチレンソルビトール脂肪酸エステル等の非イオン界面活性剤が挙げられ、粉体としてはタルク、セリサイト、マイカ、カオリン、シリカ、ベントナイト、バーミキュライト、亜鉛華、雲母、雲母チタン、酸化チタン、酸化マグネシウム、酸化ジルコニウム、硫酸バリウム、ベンガラ、酸化鉄、群青等が挙げられ、pH調整剤としては乳酸－乳酸ナトリウム、クエン酸－クエン酸ナトリウム等の緩衝剤が挙げられる。また種々の有効成分として、アラントイン、ビタミンEアセテート、グリチルリチン、ヨクイニン、各種植物抽出物等を添加することにより、メラニン抑制効果の向上を図ることができる。更に、種々の紫外線吸収物質を添加することにより、日焼けの予防効果と治療効果を兼ね備えた化粧料とすることもできる。

【００１８】本発明の美白化粧料は、紫外線による皮膚の炎症、しみ、そばかす、日焼け後の色素沈着部等の患部に局所的に適用することにより、該部位を治療・改善し、正常な皮膚色に戻すことができる。また、一般にその用量は、例えばクリーム状又は軟膏状の製剤の場合、皮膚面1cm^2当り1～20mg、液状製剤の場合、同じく1～10mgとするのが好ましい。

【００１９】

【実施例】次に、実施例および参考例をあげて本発明を説明する。

【００２０】参考例1

4-ヒドロキシ-2-メトキシ桂皮酸エチルエステルの合成：4-ヒドロキシ-2-メトキシベンズアルデヒド0.5g（3.3mmol）をベンゼン23mlに溶かし、室温下（カルベトキシメチレン）トリフェニルフォスフォラン1.64g（4.7mmol）を1時間かけて加え、その状態で3時間撹拌を続けた。反応終了後、ベンゼンをエバポレーターで留去したのち、残留物をカラムクロマトグラフィ（シリカゲル）にかけて精製し、粗精製物0.7gを得た。これを水－エタノールより再結晶化し、融点143.1～146.0℃の白色針状晶として4-ヒドロキシ-2-メトキシ桂皮酸エチルエステル496mg（2.2mmol）を得た（収率68%）。

IR(KBr,cm^{-1})

3364(s), 3080, 2980, 2944, 1682(s),1610(s), 1582(s), 1480, 1436,1372, 1350, 1312(s), 1286, 1238, 1186(s),1168, 1112, 1038, 988,960, 860, 800, 672, 652, 518, 470

^{1}H-NMR($CDCl_3$+D_2O,TMS,δ)

7.90(1H,d,J=16.1Hz), 7.37(1H,d,J=9.0Hz), 6.5-6.3(3H),4.25(2H,q,J=7.2Hz), 3.85(3H,s), 1.33(3H,t,J=7.2Hz),

【００２１】実施例1

4-アセトキシ-2-メトキシ桂皮酸エチルエステルの合成：4-ヒドロキシ-2-メトキシ桂皮酸エチルエステル300mg（1.35mmol）、無水酢酸220mg（2.15mmol）とピリジン1.07gの混合物を室温で一晩撹拌した。これに水10mlを加え、酢酸エチル20mlで2回抽出し、硫酸マグネシウムで乾燥した。溶媒をエバポレーターで留去したのち、残留物をカラムクロマトグラフィー（SiO_2，ヘキサン／酢酸エチル＝5）にかけて精製し、融点56.4～57.0℃の白色結晶として4-アセトキシ-2-メトキシ桂皮酸エチル

5　　6

エステル341mg（1.29mmol）を得た（収率96%）。

^{1}H-NMR(CDCl$_3$,TMS,δ)

7.92(1H,d,J=16.1Hz), 7.50(1H,d,J=8.3Hz), 6.8-6.6(2H),6.49(1H,d,J=16.1Hz), 4.26(1H,q,J=7.2Hz), 3.87(3H,s),2.31(3H,s),1.33(3H,t,J=7.2Hz)

【００２２】実施例２

4-アセトキシ-2-メトキシ桂皮酸及び4-ヒドロキシ-2-メトキシ桂皮酸の合成：4-アセトキシ-2-メトキシベンズアルデヒド0.86ｇ（4.43mmol）、マロン酸1.15ｇ（11.1mmol）、ピリジン４mlおよびピペリジン１滴の混合物を1.5時間加熱撹拌した。冷却後、水30mlを加えて30分間撹拌後、析出した結晶を沪取した。第１晶からは、融点187.1～193.4℃の白色結晶として4-アセトキシ-2-メトキシ桂皮酸295mg（1.25mmol）を得た（収率28%）。

^{1}H-NMR(DMSOd$_6$,TMS,δ)

12.34(1H,brs), 7.78(1H,d,J=16.1Hz),7.72(1H,d,J=8.5Hz), 6.91(1H,s),6.77(1H,d,J=8.5Hz), 6.50(1H,d,J=16.1Hz), 3.85(3H,s), 2.28(3H,s)

また、第２晶からは、4-アセトキシ-2-メトキシ桂皮酸＊と4-ヒドロキシ-2-メトキシ桂皮酸の混合物399mgを得た。続いて、この混合物399mgとナトリウムメチラート200mg（3.70mmol）のメタノール溶液を30分間加熱撹拌した。冷却後、飽和塩化アンモニウム水溶液を加えて酸性にしたのち、テトラヒドロフラン20mlで抽出した。溶媒をエバポレーターで留去したのち、エーテルに溶解し、飽和炭酸水素ナトリウム水溶液を加え有機層を分離した。水層に希塩酸を加えて酸性にしたのち、析出した黄緑色結晶を沪取した。これを水－アセトンより再結晶化し、融点165.5～167.5℃（分解）の微黄色粉末として4-ヒドロキシ-2-メトキシ桂皮酸114.6mg（0.52mmol）を得た（収率は4-アセトキシ-2-メトキシベンズアルデヒドに対して12%）。

^{1}H-NMR(DMSOd$_6$,TMS,δ)

10.12(1H,brs), 7.73(1H,d,J=16.1Hz),7.49(1H,d,J=8.3Hz), 6.44(1H,s),6.40(1H,d,J=8.3Hz), 6.29(1H,d,J=16.1Hz), 3.80(3H,s)

【００２３】実施例３

化粧水型化粧料：

（組成）

4-アセトキシ-2-メトキシ桂皮酸エチルエステル	5.0(重量%)
グリセリン	4.0
ポリオキシエチレン硬化ヒマシ油	1.5
エタノール	10.0
ピロリドンカルボン酸ナトリウム	2.0
香料	微量
精製水	残量
合計	100.0

【００２４】実施例４

オイルエッセンス型化粧料：

（組成）

4-アセトキシ-2-メトキシ桂皮酸エチルエステル	5.0(重量%)
ミンク油	55.0
小麦胚芽油	40.0
合計	100.0

【００２５】実施例５

W/O型モイスチャークリーム型化粧料：

（組成）

4-アセトキシ-2-メトキシ桂皮酸	5.0(重量%)
ワセリン	6.0
コレステロール	0.6
セタノール	0.5
ソルビタンセスキオレート	2.0
液状ラノリン	4.0
イソプロピルパルミテート	8.0
スクワレン	10.0
固型パラフィン	4.0
ブチルパラベン	0.1
メチルパラベン	0.1

7

グリセリン	3.0
香料	0.2
精製水	バランス
合計	100.0

【００２６】実施例6

O/W型モイスチャークリーム型化粧料：

（組成）

4-ヒドロキシ-2-メトキシ桂皮酸エチルエステル	5.0(重量%)
ステアリン酸	2.0
セタノール	4.0
ワセリン	5.0
スクワレン	8.0
硬化パーム油	4.0
ポリオキシエチレンソルビタンモノステアレート(20E.O.)	1.4
親油型モノステアリン酸グリセリン	2.4
ブチルパラベン	0.1
メチルパラベン	0.1
グリセリン	3.0
ジプロピレングリコール	3.0
L-アルギニン10.0(%)水酸化カリウム	0.2
香料	0.2
精製水	バランス
合計	100.0

【００２７】実施例7

乳液型化粧料：

（組成）

4-ヒドロキシ-2-メトキシ桂皮酸エチルエステル	5.0(重量%)
ステアリン酸	1.0
セタノール	2.0
ワセリン	2.5
スクワレン	4.0
硬化パーム油	2.0
ポリオキシエチレンソルビタンモノステアレート(20E.O.)	1.4
親油型モノステアリン酸グリセリン	1.2
ブチルパラベン	0.1
メチルパラベン	0.1
グリセリン	3.0
ジプロピレングリコール	3.0
水酸化カリウム	0.2
カルボキシビニルポリマー	0.2
香料	0.2
精製水	バランス
合計	100.0

【００２８】実施例8

パック型化粧料（ペースト状ピールオフタイプ）：

（組成）

4-ヒドロキシ-2-メトキシ桂皮酸	10.0(重量%)
ポリビニルアルコール	12.0
カルボキシメチルセルロースナトリウム	3.0
ジプロピレングリコール	2.0

グリセリン	2.0
エタノール	5.0
オリーブ油	3.0
ポリオキシエチレン硬化ヒマシ油（30E.O.）	0.5
酸化チタン	8.0
カオリン	6.0
香料	0.1
メチルパラベン	0.1
精製水	バランス
合計	100.0

【００２９】実施例9

軟膏型化粧料：

（組成）

4-アセトキシ-2-メトキシ桂皮酸エチルエステル	10.0(重量%)
白色ワセリン	90.0
合計	100.0

【００３０】実施例10

液剤型化粧料：

（組成）

4-アセトキシ-2-メトキシ桂皮酸エチルエステル	5.0(重量%)
エタノール	95.0
合計	100.0

【００３１】試験例1

マウス背部皮膚毛包器官培養系のチロシナーゼ活性による評価

試験方法：メラニン合成を盛んに行っている生後８～11日のC57BL系マウスの背部毛包を３～４日間培養した。培養中の培養液に評価サンプルを最終濃度５mMになるように添加し、メラニン合成を担う酵素・チロシナーゼ活性を3,5-^{3}H-チロシンからの遊離トリチウム量（^{3}HOH）により測定し、コントロールと比較し評価した。その結果を表１に示す。

＊

抑制効果	
なし	0
0～5%	±
5～35%	+
35%～	++

結果：

【００３２】

【表１】

	抑制効果
4-ヒドロキシ-2-メトキシ桂皮酸エチルエステル	+
4-アセトキシ-2-メトキシ桂皮酸エチルエステル	++
4-ヒドロキシ-2-メトキシ桂皮酸	±
4-アセトキシ-2-メトキシ桂皮酸	±
p-ヒドロキシ桂皮酸（比較例）	0

【００３３】試験例2

後天的なメラニン色素斑形成能を有する褐色モルモットを実験動物として用い、色素沈着を形成後、色素沈着に対する退色改善効果を調べた。

試験方法：褐色モルモット（皮膚色が黄色人種のものと類似し、人間と同様紫外線の照射後約４日で色素斑が生じ始め、約８日間に最も黒化するモルモット）を用い、該モルモットの背部毛をバリカンにて刈毛し、更に電気※カミソリにて剃毛した。このモルモットに8-メトキシソラレン（PUVA）を腹腔内投与後、UVA（BLBランプ，3.1mW/cm^{2}）を５分間照射した。照射15日後より、生じたPUVA色素斑形成部位に評価サンプル（4-アセトキシ-2-メトキシ桂皮酸エチルエステル）の５%溶液（エタノール80%，水20%）を１日２回計30日間連続して塗布した。皮膚色の黒化度は以下に示す判定規準にて肉眼判定し、評価点を平均しその効果を測定した。この結果を表２に示

す。

判定規準

0：色素沈着を認めない。

1：境界不明瞭なわずかな色素沈着を認める。

2：境界明瞭な中程度の色素沈着を認める。

＊3：境界明瞭な強度の色素沈着を認める。

結果：

【0034】

【表2】

＊

	塗布前	30日後
4-アセトキシ-2-メトキシ桂皮酸エチルエステル	2.5	1.4
対照（エタノールのみを塗布）	2.4	2.2

【0035】

【発明の効果】本発明の美白化粧料は、色素沈着改善効果に優れ、予め日焼けを防止する従来のサンスクリーン剤等とは異なり、皮膚のしみ、そばかす、日焼け後の色素沈着部に局所的に適用することにより、該部位を治療※・改善し、正常な皮膚色に戻すことができるものである。また、有効成分である本発明の桂皮酸エステル誘導体(1)は、皮膚に対する刺激性、アレルギーの発現等が認められず、本発明の美白化粧料は安全性の高いものである。

フロントページの続き

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